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Paradigm Shift for Endometriosis and the Potential Role of Genetic Testing – Going Beyond the 2022 ESHRE Guidelines for Endometriosis

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ABSTRACT

Endometriosis is a chronic inflammatory gynecological disease affecting 190 million women or 10% of women of reproductive age worldwide. The disease is marked by the presence of endometrial-like tissue outside the uterus, being associated in many cases with chronic pain and infertility. The current recommendations of international professional societies underline the need for laparoscopy, eventually followed by histological verification, as the gold standard for diagnosis. However, many societies recommend the initiation of specific treatment before obtaining a definitive surgical diagnosis. Various national and international societies have released guidelines for endometriosis assessment based on biomarkers; however, none of these recommendations proved to be clinically useful or able to replace diagnostic laparoscopy. In recent years it was demonstrated that oxidative stress, defined as an imbalance between reactive oxygen species and antioxidants that is directly linked with an increased inflammatory response in the peritoneal cavity, may be involved in the pathophysiology of endometriosis. The identification of a genetic predisposition for endometriosis can identify the patients at risk and may help clinicians promptly initiate therapeutic management of their patients in order to ameliorate their prognosis.

Keywords: endometriosis, laparoscopy, biomarkers, oxidative stress

Endometriosis is a chronic inflammatory condition associated with severe pain and subfertility affecting approximately 190 million women and adolescent girls worldwide.[1,2] It is a complex disease of controversial etiology, defined by the presence of endometrial-like tissue outside the uterus. The socioeconomic burden of endometriosis, which affects not only the women with the disease but also their partners, may be similar to Crohn's disease, diabetes, and rheumatoid arthritis, mostly because of the associated infertility and the way it affects the patient's quality of life including work, education, social and intimate life, and general

wellbeing.[3–6] Furthermore, the average time from symptom onset to diagnosis is currently between 8 to 12 years, which may be explained by the lack of clearly established or accurate noninvasive diagnostic tests or biomarkers.

Treatment options for endometriosis include: 1) surgical treatment, consisting in the surgical removal of endometriotic lesions and adhesions; 2) hormonal treatment, which suppresses endogenous estrogen levels and has proapoptotic and anti-inflammatory effects on endometriotic tissues; 3) the management of chronic pain.[1–6]

The European Society of Human Reproduction and Embryology (ESHRE) has published a series of evidence-based recommendations in their 2022 guideline on the care of women with endometriosis. While the role of these recommendations is clearly established, there is a significant unmet clinical need to improve many aspects related to the diagnosis and treatment of this condition.[6] The aim of this paper is to challenge the current paradigm of laparoscopic identification of endometriotic lesions with histological verification as the gold standard for the diagnosis of endometriosis.

Routinely used in many countries for the diagnosis of endometriosis, laparoscopy is an invasive surgical procedure that requires general anesthesia and is associated with morbidity and even mortality.[7–10] However, given the improvements in the technological caliber and accessibility of imaging modalities for some types of endometriosis on the one hand, and the risks and costs associated with surgery, as well as the difficulty of accessing highly skilled surgeons on the other, there is an urgent need for a revision of this paradigm. Furthermore, it is crucial to develop new noninvasive techniques and improve those that already exist in order to accurately diagnose or rule out endometriosis.[6–8]

Several biomarkers have been proposed for the early, noninvasive diagnosis of endometriosis, but their efficiency has to be demonstrated in clinical studies with adequate outcome measurement and standardized biological sample collection and storage protocols.[6,11,12] So far, the results of the studies assessing the use of these biomarkers in the diagnosis of endometriosis have been disappointing.[6,12,13]

Some of the biomarkers proposed for the diagnosis of endometriosis, such as neuronal marker protein gene product 9.5 (PGP 9.5), vasoactive intestinal polypeptide (VIP), substance P (SP), neuropeptide Y (NPY), or calcitonin gene-related peptide (CGRP), are used to differentiate ovarian endometrioma from other ovarian tumors. However, the available evidence does not support their use for the diagnosis of endometriosis.[6,12–14]

Another proposed biomarker is cancer antigen 125 (CA-125), an inexpensive and widely available tumor marker. A systematic review of 19 prospective and 3 retrospective observational studies involving 3,626 participants with histologically confirmed endometriosis found a specificity of 93% but a sensitivity of only 52% for endometriosis.[6,15] Evidence suggests that CA-125 can be used as a screening marker in symptomatic patients, but its low sensitivity means that a negative result does not rule out endometriosis,[6] and a positive result may cause anxiety for the patient and increase the risk of overtreatment. As a result, studies suggest that CA-125 should not be used routinely for the diagnosis of endometriosis.[6]

Other studies, investigating the clinical usefulness of miRNAs (known to control genes involved in the etiology of endometriosis) as biomarkers of endometriosis, have also yielded mixed results.[6,16,17]

Overall, evidence suggests that currently there are no biological markers that can reliably aid the diagnosis of endometriosis. Therefore, the authors of the 2022 ESHRE guideline concluded that "clinicians should not use measurement of biomarkers in endometrial tissue, blood, menstrual or uterine fluids to diagnose endometriosis."[6] This makes genetic testing linked to the pathogenic process of endometriosis an intriguing area of study.[18,19]

Recent studies have focused on other factors that may contribute to the development of endometriotic lesions such as familiar propensity and genetic predisposition. The pathophysiology of endometriosis may involve oxidative stress, an imbalance between reactive oxygen species and antioxidants that results in a general inflammatory response in the peritoneal cavity.[19] Reactive oxygen species are intermediaries produced by the normal oxygen metabolism and are inflammatory mediators known to modulate cell proliferation and to have deleterious effects.[19]

One of our previous studies sought to determine whether there was a relationship between endometriosis-related infertility and four genetic variants of antioxidant enzymes involved in oxidative stress.[18] In this case-control study, the first of this kind in Eastern European women, we investigated the genetic polymorphism of four genes and selected those that encode antioxidant enzymes involved in oxidative stress: glutathione peroxidase 1, GPX1 198Pro > Leu, catalase CAT-262C > T, glutathione S-transferase M1, and T1 null genotype. We investigated the association between these polymorphisms and endometriosis-related infertility in 103 patients with endometriosis-associated infertility and a control group of 102 post-partum women. The variant genotypes were significantly more frequent in the endometriosis group for the CAT-262C > T polymorphism, and the CT and TT genotypes were also significantly more frequent compared in the endometriosis group in respect

to the GPX1 198Pro > Leu. The null genotype of GSTM1 was also detected with a significantly higher frequency in the endometriosis group. However, there were no significant differences between the two groups in respect to the frequency of GSTT1. These results suggested that GPX1 198Pro > Leu, CAT-262C > T, and GSTM1 polymorphisms may predispose patients to develop endometriosis, the association between the GSTM1-GSTT1 null genotype may play a significant role in endometriosis-associated infertility, and the GSTT1 null genotype does not influence the disease.[18] These results are in accordance with two meta-analyses that also concluded that the association of both null genotypes for GSTT1-GSTM1 may be related to endometriosis.[20,21] Given that ethnicity and environmental factors play a significant role in the development endometriosis, some of our findings that are in contrast with data from the literature may be explained by demographic variances.[18]

Therefore, the question arises: is it time to stop using microscopic confirmation of endometriotic lesions as the gold standard for diagnosing endometriosis? Looking at the published results on biomarkers it is hard to declare that this approach is obsolete. For the early diagnosis of this condition, a panel of genetic or laboratory markers is required, especially in the case of young patients who intend to become pregnant in the future. Besides the conventional treatment methods, the management of endometriosis should include strategies that involve the community and ensure a higher quality of life for these patients. These strategies should focus on the establishment of readily available integrated services that increase the standard of care for women with endometriosis, beginning from adolescence.

Over the years, laparoscopy has become the gold standard method for the diagnosis of endometriosis. The preferred method to replace laparoscopy would have to be noninvasive, dependable, and affordable, with good sensitivity and specificity. Large-scale international, multicenter investigations with independent validation using cutting-edge technological platforms, thorough standardized phenotyping, and sufficient financing are urgently needed to move away from the reliance on invasive diagnostic methods like laparoscopy under general anesthesia.

CONFLICT OF INTEREST

Nothing to declare.

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